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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,794	04/08/2005	Francis Thomas Boyle	100864-1P US	4278

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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	
MAIL DATE	DELIVERY MODE
11/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,794	BOYLE ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6,7 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6,7 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 pages / 10/23/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on October 23, 2009.

Status of claims

Amendment of claims 1 and 4; and cancellation of claims 2, 15, 17-19 and 23 is acknowledged.

Claims 1, 3-4, 6-7 and 15 are pending and are the subject of this office action.

Claims 1, 3-4, 6-7 and 15 are presently under examination.

The following species are being examined: ZD4054 (Zibotentan) as the endothelin receptor antagonist, and ZD1839 (Iressa-Gefitinib) as the EGFR TKI.

Priority

The present application claims priority to application No. PCT/GB03/04347 filed 10/07/2003, which claims priority to foreign application No. UNITED KINGDOM 0223854.1 filed on 10/12/2002.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not

Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103 (Maintained rejection)

Claims 1, 3-4, 6-7 and 15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Fujimura et. al. (Clinical Cancer Research (July 2002) 8:2448-2454, cited in prior office action), Salani et. al. (Clinical Science (August 2002) 103 (Suppl. 48) 318S-321S, cited in prior office action), and Bradbury et. al. (US 6,258,817, cited in prior office action).

The reasons for this rejection have been provided in the previous office action dated June 26, 2009, the text of which is incorporated by reference herein.

Applicant's arguments have been fully considered but are not persuasive.

Applicant argues that: the Examiner has not met the appropriate burden to establish a prima facie case for obviousness, particularly for the claims as amended. In this regard, with respect to the combination of the teachings of Fujimura et al., Salani et al. and Bradbury et al, Applicants posit the question: what would motivate the ordinarily skilled artisan to combine these references? Applicants respectfully assert that Bradbury et al. is only one patent application out of a multitude of prior art that discloses endothelin antagonists. In order to arrive at the teaching of the present invention the ordinarily skilled artisan would have to:

1) select Bradbury et al. from all the prior art on endothelin antagonists; then

2) select Compound (I) from the 70 Examples in Bradbury et al. when there is nothing in Bradbury that particularly highlights this compound as being of interest; then

3) select the two particular references of Fujimura et al. and Salani et al. from the vast array of prior art on endothelin antagonists; and then

4) decide to combine the teaching of Bradbury et al. with the teachings of both of these references.

In this regard, Applicants assert that the ordinarily skilled person would not take these steps; and even if the ordinarily skilled person did take these steps, the ordinarily skilled person would have no reasonable expectation of success. It is only with the benefit of hindsight that the Examiner can make this allegation; and such hindsight, again, is impermissible. In fact, there is nothing in any of the cited references that would guide the ordinarily skilled artisan to particularly select the other two references and combine them in such a way to arrive at the present invention.

Furthermore, Applicants respectfully assert that the role of endothelin-1 (ET-1) in cancer is not as simplistic as the story laid out in the Office Action. Endothelin antagonists act by inhibiting the binding of ET-1 at its receptors. There are two receptors - ETA and ETR. More importantly, there is emerging evidence that the ETB receptor is involved in apoptotic signalling, and that ET-1 acting at the ETB receptor may actually provide a beneficial pathway in oncology by regulating apoptosis and by clearing excess ET-1. In this regard, we remind the Examiner that apoptosis is a natural process of self-destruction in certain cells, i.e., programmed cell death. It would,

therefore, obviously be an undesirable property of an oncology compound to interfere or stop the process of apoptosis.

In fact, it is the inhibition of ET-1 acting at the ETA receptor that has been considered an important mode of action in the management of certain cancers. The blocking of pro-apoptotic pathways would be undesirable in the treatment of cancer; hence a compound that specifically targeted the ETA receptor while leaving the ETB receptor unaffected would be of the greatest utility in the treatment of cancer. ZD4054 is such a compound.

The Examiners attention is further drawn to the enclosed article (cited in the co-filed SB/08 Form) from Nature Reviews Urology 6, 350 (July 2009) entitled "Prostate cancer: New endothelin-A receptor antagonist prolongs survival". This article discusses ZD4054 and the Phase II clinical trial results, and asserts that the compound has been "shown to improve the overall survival of men with hormone-resistant metastatic prostate cancer" (emphasis added). This article also contrasts ZD4054 with Atrasentan (ABT-627), another endothelin antagonist in clinical trials that has not shown the overall survival benefit:

Atrasentan, another selective endothelin-A receptor antagonist, has a positive impact on PSA-based progression and markers of bone involvement. Failure of this drug to improve overall survival in a phase III trial may be due to the fact that it also inhibits signaling mediated by the endothelin-B receptor, which is thought to promote apoptosis and slow tumor spread. ZD4054 seems to have the advantage of not inhibiting endothelin-B receptor activity.

As such, and particularly in light of these findings, the fact that ZD4054 is such a suitable agent for use in treating cancer could not have been predicted from any of the prior art teachings, particularly when known selective endothelin A antagonists have measurable, undesirable, endothelin B properties.

Thus, not only would the ordinarily skilled person not have selected ZD4054 nor tested it in an ovarian model, from the cited prior art, the skilled person could not have predicted that ZD4054 would be such a suitable agent for this use.

Examiner's response: Salani teaches that endothelin-I (ET-I) is present at high concentrations in ovarian cancer ascites and is overexpressed in primary and metastatic ovarian carcinomas and it is clearly associated with the development and growth of these tumors (see abstract). ET-I acts selectively through the receptor ET_A, which is predominantly expressed in tumor cells. Salani further demonstrates that activation of the ET_A in ovarian carcinoma cells promotes cell proliferation, neovascularization and invasion, which are the principal hallmarks of malignant transformation. The present study was designated to investigate the effects of the ET_A-selective antagonist ABT-627 on the ET-I induced mitogenic effect in both primary cultures (PMOVI and PMOV2) and cell lines (OVCA 433 and HEY) of ovarian carcinoma. All tumor cells express the components of the ET-I system and secrete ET-I. ET_A blockade by ABT-627 inhibits ET-I-induced mitogenic effects. The ET_B antagonist BQ-788 is ineffective although cell lines express both ET_A and ET_B mRNAs (see abstract).

From the above teachings it is concluded that antagonists of the ET_A receptor are effective in the treatment of ovarian cancer and that antagonists of the ET_B receptor have no effect. So at the time of the invention, the skilled in the art would have been motivated to treat ovarian cancer with any ET_A antagonist, regardless of its effect on the ET_B receptor, since the prior art teaches that ET_A antagonism is definitively required but ET_B antagonism has no effect. The skilled in the art would have been motivated to pick any endothelin (ET) receptor antagonist disclosed in the prior art that has some ET_A antagonism like for example the ones disclosed by Bradbury et. al. since it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (any endothelin receptor antagonist that has some ET_A anatgonism) for another (ZD4054 or any of the other ones disclosed by Bradbury) with an expectation of success, since the prior art establishes that both function in similar manner.

Regarding the reference presented by Applicant: Nature Reviews in Urology (2009) 6:350, there is nothing that shows any difference between these two compounds regarding their efficacy in treating ovarian cancer. The reference deals with a different type of cancer: prostate cancer. Second, the reference states: "failure of this drug (ABT-627) to improve overall survival in phase III trial may be due to the fact that it also inhibits signaling mediated by the ET_B receptor". The word may indicates that the statement is merely speculative and an invitation for further research. In other words, it is not known if ABT-627 actually antagonizes the ET_B receptor or even if it does, if this is the reason for not improving the efficacy in treating prostate cancer.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571 272-0580. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
November 12, 2009

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612